

**A New Modeling Approach to Biochemical Networks, With an Application to Oxidative Stress in Yeast**  
**Mendes, Pedro , Shulaev, Vladimir, Laubenbacher, Reinhard**  
**Virginia Bioinformatics Institute, Virginia Tech, Blacksburg, VA, USA**

A hybrid approach to constructing mathematical models using continuous and discrete mathematical methods is under development in our laboratories. The objective is to be able to use time series data of mRNA, protein, and metabolite levels, to reconstruct the underlying biochemical networks and dynamics. Our strategy is to first apply methods from dynamics and discrete mathematics independently to obtain preliminary models of the observed dynamics. Then a consensus model is developed which combines the characteristics of the individual continuous and discrete methods. This allows for recovering high-value information from relatively small data sets.

To reconstruct the underlying dynamics of a time series assuming continuous time, we make use of a linear approximation to dynamical systems, namely the Jacobian matrix of partial derivatives of the ODEs, which we see as a first approximation to the interaction network. We have developed a method to reconstruct a qualitative version of this matrix from a minimal set of time series data, which is limited to revealing the pairs of molecules that do *not* interact. This is very important since it reduces the dimensionality of the problem drastically (most known systems have sparse Jacobians). A second stage uses least-squares methods to fit a set of differential equations to the time series data, producing a quantitative model of the system.

The next step in the modeling approach is to simplify the system further by categorizing the experimental data into a finite collection of values, a common method in statistics, in order to deal with noise. Applying this method to the states of our time-discrete approximation of the biochemical system under study, we obtain a time-discrete dynamical system with a finite state set. If we now choose our finite state set in such a way that it supports standard arithmetic, commonly known as modular arithmetic, then the system can be described via polynomial functions. We are then in a position to bring to bear the power of the well-developed machinery of computational polynomial algebra. It allows us to study the whole space of models consistent with the given data, and we have developed methods for model selection that work particularly well with the mutant data to be collected for this project. The results obtained from this modeling approach are then combined with the ODE models described above.

To develop this modeling strategy and to demonstrate its utility, we are collecting data about the response of *S. cerevisiae* to oxidative stress. This consists of collecting time series data on *i*) mRNA levels, using Affymetrix™ chips, *ii*) protein levels, using 2D gels and MALDI-MS, and *iii*) metabolite levels, using GC-MS and LC-MS. These data are collected after perturbing the microbial culture with the oxidant cumene hydroperoxide. Nine time series are collected for the wild type strain and 8 null mutants with isogenic background. The mutant data is needed for validation of the models. We are also investigating how the use of mutant data may improve the process of constructing the models.

*This work is supported by grants from the National Institutes of Health (GM068947-01) and National Science Foundation (DBI-0109732).*